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(1) a gene encoding a mouse mutant presenilin-1 protein having an amino acid sequence as set forth in SEQ ID NOS: 1 or 3 wherein the isoleucine at position 213 is substituted with an amino acid other than isoleucine; and

(2) a neomycine expression unit flanked by loxPs.

35. (Twice Amended) The method according to claim 34, wherein a mutant presenilin-1 protein having an amino acid sequence as set forth in SEQ ID NOS: 1 or 3 is expressed in which the isoleucine at position 213 is substituted with an amino acid other than isoleucine.

REMARKS

The Examiner is respectfully requested to enter the foregoing amendment prior to examination of the above-identified patent application. The foregoing amendments are made to insert SEQ ID NOS: in the claims in accordance with the Notice to Comply mailed from the U.S.P.T.O. on July 22, 2002, and are not intended to, nor should they be construed as narrowing the scope of the claims.

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If there are any comments or questions, the undersigned may be contacted at the below-listed telephone number.

Respectfully Submitted,
Masatoshi TAKEDA et al.

Bruce H. Bernstein
Reg. No. 29,027

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GREENBLUM & BERNSTEIN, P.L.C.
1941 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

MARKED UP COPY OF AMENDED CLAIMS

2. (Amended) The gene-mutated animal according to claim 1, wherein the animal has a mutant presenilin-1 gene which comprises a DNA [having a] sequence as set forth in SEQ ID NOS: 2 or 4 encoding a presenilin-1 protein in which an amino acid in the amino acid sequence set forth in SEQ ID NOS: 1 or 3 is substituted [of the presenilin-1 protein is substituted with a different amino acid].

3. (Amended) A non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA [having a] sequence as set forth in SEQ ID NOS: 2 or 4 encoding a mutant presenilin-1 protein which has [an amino acid sequence in which] one or more amino acid[s] substitutions in the amino acid sequence as set forth in SEQ ID NOS: 1 or 3 at positions [selected from the group consisting of amino acid numbers] 79, 82, 96, 115, 120, 135, 139, 143, 146, 163, 209, 213, 231, 235, 246, 250, 260, 263, 264, 267, 269, 280, 285, 286, 290, 318, 384, 392, 410, 426, [and] or 436 [is substituted with different amino acid(s) in the amino acid sequences of presenilin-1 protein].

4. (Amended) A non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA [having a] sequence as set forth in SEQ ID NOS: 2 or 4 encoding a mutant presenilin-1 protein which has one or more [mutations] amino acid substitutions in the amino acid sequence as set forth in SEQ ID NOS: 1 or 3 selected from the group consisting of A79V, V82L, V96F, Y115H, Y115C, E120K, E120D, N135D, M139V, M139T, M139I, I143F, I143T, M146L, M146V, H163Y, H163R, G209V, I213T, A231T, A231V, L235P, A246E, L250S, A260V, C263R, P264L, P267S, [R269G], R269G, R269H, E280A, E280G, A285V, L286V, S290C, E318G, G384A,

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L392V, C410Y, A426P [and] or P436S [in the amino acid sequence of presenilin-1 protein, wherein each alphabet represents an amino acid expressed as a one-letter symbol, each number represents an amino acid number from the N-terminus of the presenilin-1 protein, and the descriptions mean that a wild-type amino acid shown in the left of the numerical figure is substituted with an amino acid shown in the right].

5. (Amended) A non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA having a sequence as set forth in SEQ ID NOS: 2 or 4 encoding a mutant presenilin-1 protein in which the isoleucine at position 213 of a presenilin-1 [protein] amino acid sequence as set forth in SEQ ID NOS: 1 or 3 is substituted with an amino acid other than isoleucine.

6. (Amended) A non-human gene-mutated animal having a mutant presenilin-1 gene which comprises a DNA having a sequence as set forth in SEQ ID NOS: 2 or 4 encoding a mutant presenilin-1 [protein] amino acid sequence as set forth in SEQ ID NOS: 1 or 3 in which the isoleucine at position 213 [of a presenilin-1 protein] is substituted with threonine.

7. (Twice Amended) The non-human gene-mutated animal according to claim 1, [wherein the animal has the mutant presenilin-1 gene] wherein a DNA sequence as set forth in SEQ ID NOS: 2 or 4 [encoding around an amino acid at position 213 in an amino acid sequence of the presenilin-1 protein] is mutated around base pair 639 to the following sequence:

5'-TGTGGTCGGGATGATMGCC ANC CACTGGAAAGGCC-3'

wherein N represents a base other than T, M represents T or C, and the underlined bases encode the amino acid at position 213 of the amino acid sequence set forth in SEQ ID NOS: 1 or 3.

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8. (Twice Amended) The non-human gene-mutated animal according to claim 1, [wherein the animal has the mutant presenilin-1 gene] wherein a DNA sequence as set forth in SEQ ID NOS: 2 or 4 [encoding around an amino acid at position 213 in an amino acid sequence of the presenilin-1 protein] is mutated around base pair 639 to the following sequence:

5'-TGTGGTCGGGATGATMGCC ANC CACTGGAAAGGCCC-3'

wherein N represents C, M represents T or C, and the underlined bases encode the amino acid at position 213 of the amino acid sequence set forth in SEQ ID NOS: 1 or 3.

9. (Twice Amended) The non-human gene-mutated animal according to claim 1, [wherein the animal has the mutant presenilin-1 gene] wherein a DNA sequence as set forth in SEQ ID NOS: 2 or 4 [encoding around an amino acid at position 213 in an amino acid sequence of the presenilin-1 protein] is mutated around base pair 639 to the following sequence:

5'-TGTGGTCGGGATGATMGCC XYZ CACTGGAAAGGCCC-3'

wherein XYZ represents a codon as triplet bases which encodes an amino acids other than isoleucine, M represents T or C, and the underlined bases encode the amino acid at position 213 of the amino acid sequence set forth in SEQ ID NOS: 1 or 3.

19. (Amended) A plasmid comprising a DNA or a part thereof, wherein said DNA has a sequence as set forth in SEQ ID NOS: 2 or 4 [of a mutant presenilin-1 gene] wherein [a DNA] the sequence [encoding around an amino acid at position 213 of an amino acid sequence of a presenilin-1 protein] is mutated around base pair 639 to the following sequence:

5'-TGTGGTCGGGATGATMGCC ANC CACTGGAAAGGCCC-3'

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wherein N represents A, G, or C, M represents T or C, and the underlined bases encode an amino acid at position 213 of the amino acid sequence set forth in SEQ ID NOS: 1 or 3.

20. (Amended) A plasmid comprising a DNA or a part thereof, wherein said DNA has a sequence as set forth in SEQ ID NOS: 2 or 4 [of a mutant presenilin-1 gene which encodes a mutant presenilin-1 protein wherein an amino acid at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a presenilin-1 protein and has a DNA sequence encoding around the amino acid at position 213 of presenilin-1 protein] wherein the sequence is mutated around base pair 639 to the following sequence:

5'-TGTGGTCGGGATGATMGCC XYZ CACTGGAAAGGCC-3'

wherein M represents T or C, XYZ denotes a codon as triplet bases encoding an amino acid other than isoleucine, and the underlined bases encode the amino acid at position 213 of the amino acid sequence set forth in SEQ ID NOS: 1 or 3.

22. (Amended) A plasmid comprising a DNA wherein a Sau3AI site is introduced into a nucleotide sequence comprising the whole or a mutated part of a cDNA or chromosomal DNA of a mutant presenilin-1 gene encoding [a mutant presenilin-1 protein in which] an amino acid set forth in SEQ ID NOS: 1 or 3 [at] wherein position 213 is substituted with an amino acid other than isoleucine [in an amino acid sequence of a presenilin-1 protein].

25. (Amended) A gene encoding a mouse mutant presenilin-1 protein having an amino acid sequence as set forth in SEQ ID NOS: 1 or 3 wherein the isoleucine at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a mouse presenilin-1 protein.

27. (Amended) A plasmid comprising:

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- (1) a gene encoding a mouse mutant presenilin-1 protein having an amino acid sequence as set forth in SEQ ID NOS: 1 or 3 wherein the isoleucine at position 213 is substituted with an amino acid other than isoleucine [in an amino acid sequence of a mouse presenilin-1 protein]; and
- (2) a neomycine expression unit flanked by loxPs.

35. (Twice Amended) The method according to claim 34, wherein a mutant presenilin-1 protein having an amino acid sequence as set forth in SEQ ID NOS: 1 or 3 is expressed in which the isoleucine at position 213 is substituted with an amino acid other than isoleucine.